

PHARMACOEPIDEMIOLOGY

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Spontaneous Reporting in the United States

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INTRODUCTION

The United States Food and Drug Administration (FDA) is the Federal public health agency that has regulatory responsibility for ensuring the safety of all marketed medical products, including pharmaceuticals (i.e., drugs and biologics) (see also Chapter 8). In order to ensure that safe and effective pharmaceuticals are available, the FDA relies on both the recognition, and *voluntary* reporting, of serious adverse events (AEs) by health care providers and their patients and the *mandatory* reporting of AEs by manufacturers as required by law and regulation.

All unsolicited reports from health care professionals or consumers, received by the FDA via either the voluntary or mandatory route, are called *spontaneous* reports. A spontaneous report is a clinical observation that originates outside of a formal study.¹ The individual spontaneous reports of adverse drug reactions (ADRs), medication errors, and product quality problems, sent directly to the FDA through the MedWatch program (see below) or to the manufacturer and then indirectly from the manufacturer to the FDA, combined with data from formal clinical studies and from the medical and scientific literature, comprise the primary data source upon which postmarketing surveillance depends. In the US,

a large majority of reports, between 70% and 75%, are submitted either directly or indirectly by health care professionals as voluntary reports, with consumer/patient reports comprising about 15% of reports.^{2,3}

In addition to this passive process for safety surveillance, the FDA continues to explore the use of new active surveillance methodologies for collecting reports of adverse effects and evaluating adverse events. The FDA may also explore drug safety questions in large population-based claim databases that link prescriptions with adverse outcomes.⁴

When the FDA approves a pharmaceutical product for prescribing and dispensing by health care providers in the United States, the agency has conducted a rigorous, science-based, multidisciplinary review of controlled clinical trials sponsored and conducted by a pharmaceutical company. The FDA has determined that the product's benefits outweigh any known or anticipated risks for the general population when the product is used as indicated in the approved prescribing information. However, the limitations inherent in the controlled clinical trial setting in the identification of rare, but clinically important, adverse events inevitably insure that uncertainties will remain about the safety of the pharmaceutical once it is marketed and used in a wider population, over longer periods of time, in patients with

comorbidities and concomitant medications, and for “off-label” uses not previously evaluated.⁵

Given these recognized and accepted limitations in the pre-approval New Drug Application (NDA) process, the agency relies on the public, both health care professionals and their patients, for the voluntary reporting of suspected, serious, and unlabeled ADRs, medication errors, and product quality problems observed during the use of the pharmaceutical in the “real-world” setting, in order to manage the risk of product use and reduce the possibility of harm to patients.

Harm to patients from pharmaceutical use may occur due to four types of risk (Figure 9.1).⁶ Most injuries and deaths associated with the use of medical products result from their *known side effects*, some unavoidable but others able to be prevented or minimized by careful product choice and use. It is estimated that more than half the side effects of pharmaceuticals are avoidable.⁷

Other sources of preventable adverse events are *medication errors*, which may occur when the product is administered incorrectly or when the wrong drug or dose is administered.

Injury from *product quality problems* is of interest to the FDA, which has regulatory responsibility for oversight of product quality control and quality assurance during the manufacturing and distribution process.

The final category of potential risk, those risks most amenable to identification by an effective voluntary reporting system, involves the *remaining uncertainties* about a product. These uncertainties include unexpected and rare AEs, long-term effects, unstudied uses and/or unstudied populations, unanticipated medication errors due to name confusion or packaging format, and product quality defects during the manufacturing process.

This chapter reviews the history of AE reporting in the United States, its terminology, and its regulatory aspects. The strengths, limitations, and applications of the FDA’s Adverse Event Reporting System (AERS) are discussed, as are future plans.

DESCRIPTION

HISTORY OF US PHARMACEUTICAL SAFETY REGULATION

The FDA is the first US consumer protection agency. Its predecessor, the Bureau of Drugs, was established in order to implement the Biologics Control Act of 1902. Subsequent drug regulatory laws, in 1906, 1938, and 1962, have all resulted from widespread public concern about drug safety and demands that the US Congress address a perceived crisis that threatened the health and lives of children. Each law or amendment incrementally strengthened the FDA’s capability to effectively monitor the postmarketing safety of drugs and other medical products.

The 1902 Act was passed by the US Congress in reaction to the public outrage from hundreds of cases of post-vaccination tetanus and the deaths of several dozen children due to tetanus-contaminated diphtheria antitoxin. This first drug safety law required annual licensing of manufacturers and distributors and the labeling of all products with the name of the manufacturer. Neither the premarketing safety and efficacy nor the post-marketing safety of these products were regulated by the government.⁸

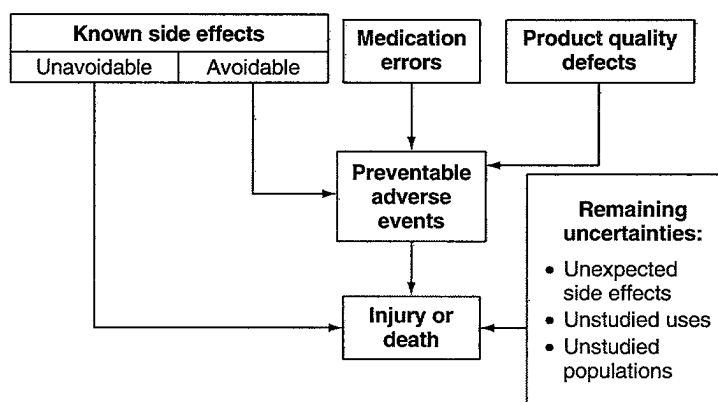


Figure 9.1. Sources of risk from medical products.

The Pure Food and Drug Act of 1906 prohibited interstate commerce of mislabeled and adulterated drugs and foods.⁹ Again, the safety of drugs after consumption was not addressed. For example, in 1934 the Agency began investigations on products containing dinitrophenol, a component in diet preparations that increased metabolic rate to dangerous levels, and was responsible for many deaths and injuries. However, the Office of Drug Control could not seize the products, and was limited to posting warnings. The safety of drugs after consumption was not addressed until the 1930s and unfortunately it was again a disaster that prompted Congress to act.¹⁰

These continuing problems with dangerous drugs that fell outside the controls of the Pure Food and Drug Act finally received national attention with the elixir of sulfanilamide disaster in 1937. The S.E. Massengill Co. introduced a flavorful oral dosage form of the new anti-infective "wonder drug" by using an untested solvent, the antifreeze diethylene glycol. By the time the FDA became aware of the problem and removed the product from pharmacy shelves and medicine cabinets, the preparation had caused 107 deaths, including many children. Even though the toxic effects of diethylene glycol were well documented by 1931, with no drug safety regulations in place, the only charge that could be brought under the 1906 Act was misbranding the product, since there was no alcohol in the "elixir," as implied by the name.

In June 1938, the Federal Food, Drug and Cosmetic Act was passed by the US Congress. The law required new drugs to be tested for safety before marketing, the results of which would be submitted to the FDA in an NDA. The law also required that drugs have adequate labeling for safe use. Again, no postmarketing safety monitoring was mandated by this new law.

During the 1950s, there was a rapid expansion of the pharmaceutical industry and an increase in the number of new products. A new broad spectrum antibiotic, chloramphenicol, was approved by the FDA in early 1949 as "safe and effective when used as indicated" (the standard for approval in the 1938 Act). However, the small number of patients exposed to chloramphenicol during pre-approval clinical trials was not adequate to observe serious but rare adverse events that would occur in fewer than 1 in 1000 patients. Within six months of approval, reports in the medical literature in the US and Europe suggested the association of fatal aplastic anemia with chloramphenicol use.

In late June 1952, in order to gather the necessary data to evaluate this issue, the FDA ordered the staff in all 16 district offices to contact every hospital, medical school, and clinic in cities with populations of 100,000 or more to collect

information on any cases of aplastic anemia or other blood dyscrasias attributed to chloramphenicol. Within four days of field contacts, an additional 217 cases of chloramphenicol-associated blood dyscrasias had been identified.¹¹

The delay in identification of and regulatory action on reports of aplastic anemia associated with chloramphenicol use demonstrated the necessity for monitoring adverse events following the approval and marketing of new drugs. In response to this need the American Medical Association (AMA) established a Committee on Blood Dyscrasias, which began collecting case reports of drug-induced blood-related illness in 1954. At that time, the AMA had a potential information source of over 7000 hospitals and 250,000 physicians. The AMA's program was expanded in 1961 to a more comprehensive "Registry on Adverse Reactions." The program was discontinued in 1971 because of parallel efforts by the FDA.¹²

In 1956, the FDA piloted its own drug ADR surveillance program in cooperation with the American Society of Hospital Pharmacists (the predecessor of the American Society of Health-System Pharmacists), the national association of medical records librarians, and the AMA.¹³ The reporting program began with 6 hospitals and by 1965 had grown to over 200 teaching hospitals which reported to the FDA on a monthly basis. In addition, reports were sent to the FDA from selected Federal hospitals (Department of Defense, Veterans Administration, Public Health Service) and published reports were culled from the medical literature and received from the World Health Organization.¹⁴

The 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act of 1938 required proof of efficacy before drug approval and marketing. For the first time, this law also mandated that pharmaceutical manufacturers must report AEs to the FDA for any of their products having an NDA, the vast majority of prescription products introduced since 1938.

The FDA began to computerize the storage of its AE reports in 1967, and by early 1968 received, coded, and entered all data from the FDA Form 1639 Drug Experience Reports into the Spontaneous Reporting System (SRS).¹⁵ The SRS was replaced in November 1997 with the Adverse Event Reporting System (AERS), a computerized information database that supports the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. AERS is an internationally compatible system designed as a pharmacovigilance tool for storing and analyzing safety reports.

By 1991, there were five different forms for manufacturers and health professionals to report medical product problems

to the agency. In 1993, then-FDA Commissioner David A. Kessler, MD, citing confusion with the multiple forms, launched the FDA's MedWatch Adverse Event Reporting Program. A single-page voluntary reporting form, FDA form 3500 (The "MedWatch" form) was introduced to report adverse events associated with all medical products except vaccines, and the FDA form 3500A was provided for use by mandatory reporters (see Figures 9.2 and 9.3). The MedWatch program was charged with the task of facilitating, supporting, and promoting the voluntary reporting process. Since 1993, over 200 000 voluntary reports have been received from health care professionals and consumers, coded, and entered into the FDA AERS database (see Figure 9.4).

REGULATORY REPORTING REQUIREMENTS

In the US, AE reporting by individual health care providers and consumers is voluntary. However, manufacturers, packers, and distributors of FDA-approved pharmaceuticals (drugs and biologic products) all have mandatory reporting requirements governed by regulation. Historically, only nonbiologic pharmaceutical products with approved NDAs (i.e., all prescription and some over-the-counter drugs) were subject to mandatory reporting requirements. In 1994, this requirement was expanded to include biologic products.¹⁶

It should be emphasized that these regulations are aimed at pharmaceutical manufacturers, but also provide a useful framework for reporting by practitioners to either the FDA and/or the manufacturer. In the US, most health professionals and consumers report AEs to the manufacturer rather than directly to the FDA. This pattern is not seen in many other countries, where consumers and health professionals report directly to a governmental public health agency.

CURRENT REQUIREMENTS

The main objective of the FDA postmarketing reporting requirement is to provide early prompt detection of signals about potentially serious, previously unknown safety problems with marketed drugs, especially with newly marketed drugs. To understand the regulatory requirements, one first needs to define several terms. These definitions are revisions that became effective in April 1998.¹⁷

An *adverse experience* is any AE associated with the use of a drug or biologic product in humans, whether or not considered product related, including the following: an AE occurring in the course of the use of the product in professional practice, an AE occurring from overdose of the product, whether accidental or intentional, an AE occurring from

abuse of the product, an AE occurring from withdrawal of the product, and any failure of expected pharmacologic action.

An *unexpected adverse experience* means any AE that is not listed in the current labeling for the product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.

A *serious adverse experience* is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Table 9.1 outlines the US mandatory reporting requirements regarding pharmaceuticals. By regulation, companies are required to report to the FDA *all* adverse events of which they become aware and to provide as complete information as possible. Although pharmaceutical reporting is mandated, it still relies primarily on information provided to them by health professionals through both voluntary reporting and the scientific literature.

In the case of over-the-counter (OTC) drugs, reports are only required on OTC products marketed under an approved NDA, including those prescription drugs that undergo a switch to OTC status. Reports are not currently required for other OTC drugs (i.e., older drug ingredients which are marketed without an NDA), although voluntary reporting is encouraged for serious events.

Both prescription and OTC drugs require FDA safety and efficacy review prior to marketing, unlike dietary supplements (which include vitamins, minerals, amino acids, botanicals, and other substances used to increase total dietary intake). By law,¹⁸ the manufacturers of these latter products do not have to prove safety or efficacy, but that same law places the responsibility on the FDA to demonstrate that a particular product is unsafe or presents a potentially serious risk to public health. In addition, manufacturers of these products do not have to report AEs to the FDA. As a result, direct-to-FDA voluntary reporting by health professionals and their patients of serious adverse events associated with and possibly causally linked to dietary supplements is particularly

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U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.**MEDWATCH**For **VOLUNTARY** reporting of
adverse events and product problemsThe FDA Safety Information and
Adverse Event Reporting Program

Page ____ of ____

FDA USE ONLY	
Triage unit	
sequence #	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: or _____ Date of Birth: _____	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or ____ kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mo/day/yr)		<input type="checkbox"/> Disability	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly	
<input type="checkbox"/> Hospitalization – initial or prolonged		<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage	
<input type="checkbox"/> Other: _____			
3. Date of Event (mo/day/year)		4. Date of This Report (mo/day/year)	
5. Describe Event or Problem			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
C. SUSPECT MEDICATION(S)			
1. Name (Give labeled strength & mfr/labeler, if known)			
#1 _____			
#2 _____			
2. Dose, Frequency & Route Used		3. Therapy Dates (If unknown, give duration) from/to (or best estimate)	
#1 _____		#1 _____	
#2 _____		#2 _____	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1 _____		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 _____		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot # (if known)	7. Exp. Date (if known)	8. Event Reappeared After Reintroduction?	
#1 _____	#1 _____	#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 _____	#2 _____	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC # (For product problems only)			
- -			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
D. SUSPECT MEDICAL DEVICE			
1. Brand Name			
2. Type of Device			
3. Manufacturer Name, City and State			
4. Model #	Lot #	5. Operator of Device	
Catalog #	Expiration Date (mo/day/yr)	<input type="checkbox"/> Health Professional	
Serial #	Other #	<input type="checkbox"/> Lay User/Patient	
		<input type="checkbox"/> Other: _____	
6. If Implanted, Give Date (mo/day/yr)		7. If Explanted, Give Date (mo/day/yr)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?			
<input type="checkbox"/> Yes <input type="checkbox"/> No			
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor			
10. Device Available for Evaluation? (Do not send to FDA)			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mo/day/yr)			
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
E. REPORTER (See confidentiality section on back)			
1. Name and Address		Phone #	
2. Health Professional?	3. Occupation	4. Also Reported to:	
<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Manufacturer	
		<input type="checkbox"/> User Facility	
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: <input type="checkbox"/>		<input type="checkbox"/> Distributor/Importer	



Mail to: **MEDWATCH** -or- FAX to:
5600 Fishers Lane 1-800-FDA-0178
Rockville, MD 20852-9787

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Figure 9.2. MedWatch voluntary reporting form (FDA Form 3500).

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ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- Medications (*drugs or biologics*)
- Medical devices (*including in-vitro diagnostics*)
- Special nutritional products (*dietary supplements, medical foods, infant formulas*)
- Cosmetics
- Medication errors

Report product problems – quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures

Report **SERIOUS** adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening (*real risk of dying*)
- Hospitalization (*initial or prolonged*)
- Disability (*significant, persistent or permanent*)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section C for all products except medical devices
- Attach additional blank pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer (*or both*)

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Important numbers:

- 1-800-FDA-0178 – To FAX report
- 1-800-FDA-1088 – To report by phone or for more information
- 1-800-822-7967 – For a VAERS form for vaccines

To Report via the Internet:

<http://www.fda.gov/medwatch/report.htm>

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

Please **DO NOT**
RETURN this form
to this address.

OMB statement:

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (12/03) (Back)

Please Use Address Provided Below – Fold in Thirds, Tape and Mail

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business

Penalty for Private Use \$300

BUSINESS REPLY MAIL

FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787



NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES
OR APO/FPO

Figure 9.2. (Continued).

SPONTANEOUS REPORTING IN THE UNITED STATES

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U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.**MEDWATCH**For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reportingThe FDA Safety Information and
Adverse Event Reporting Program

Page ____ of ____

Mfr Report #
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: or _____ Date of Birth: _____	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or ____ kgs
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mo/day/yr)		<input type="checkbox"/> Disability	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly	
<input type="checkbox"/> Hospitalization – initial or prolonged		<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage	
<input type="checkbox"/> Other: _____			
3. Date of Event (mo/day/year)		4. Date of This Report (mo/day/year)	
5. Describe Event or Problem			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
C. SUSPECT MEDICATION(S)			
1. Name (Give labeled strength & mfr/labeler, if known)			
#1 _____			
#2 _____			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1 _____		#1 _____	
#2 _____		#2 _____	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1 _____		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 _____		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot # (if known)	7. Exp. Date (if known)	8. Event Reappeared After Reintroduction?	
#1 _____	#1 _____	#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 _____	#2 _____	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC # (For product problems only)			
- -			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
D. SUSPECT MEDICAL DEVICE			
1. Brand Name			
2. Type of Device			
3. Manufacturer Name, City and State			
4. Model #	Lot #	5. Operator of Device	
Catalog #	Expiration Date (mo/day/yr)	<input type="checkbox"/> Health Professional	
Serial #	Other #	<input type="checkbox"/> Lay User/Patient	
		<input type="checkbox"/> Other: _____	
6. If Implanted, Give Date (mo/day/yr)		7. If Explanted, Give Date (mo/day/yr)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?			
<input type="checkbox"/> Yes <input type="checkbox"/> No			
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor			
10. Device Available for Evaluation? (Do not send to FDA)			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mo/day/yr)			
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA	
<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	



Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

FORM FDA 3500A (9/03)

Figure 9.3. MedWatch mandatory reporting form (FDA Form 3500A).

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**Medication and Device
Experience Report**
(Continued)

Submission of a report does not constitute
an admission that medical personnel, user
facility, importer, distributor, manufacturer
or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

Refer to guidelines for specific instructions.

Page ____ of ____

FDA USE ONLY
F. FOR USE BY USER FACILITY/IMPORTER (Devices Only)

1. Check One <input type="checkbox"/> User Facility <input type="checkbox"/> Importer		2. UF/Importer Report Number	
3. User Facility or Importer Name/Address			
4. Contact Person		5. Phone Number	
6. Date User Facility or Importer Became Aware of Event (mo/day/yr)	7. Type of Report <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up # _____	8. Date of This Report (mo/day/yr)	
9. Approximate Age of Device	10. Event Problem Codes (Refer to coding manual) Patient Code _____ Device Code _____		
11. Report Sent to FDA? <input type="checkbox"/> Yes _____ <input type="checkbox"/> No (mo/day/yr)		12. Location Where Event Occurred <input type="checkbox"/> Hospital <input type="checkbox"/> Outpatient <input type="checkbox"/> Home <input type="checkbox"/> Diagnostic Facility <input type="checkbox"/> Nursing Home <input type="checkbox"/> Ambulatory <input type="checkbox"/> Outpatient Treatment <input type="checkbox"/> Surgical Facility Facility <input type="checkbox"/> Other: _____ (Specify)	
13. Report Sent to Manufacturer? <input type="checkbox"/> Yes _____ <input type="checkbox"/> No (mo/day/yr)			
14. Manufacturer Name/Address			

G. ALL MANUFACTURERS

1. Contact Office – Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
4. Date Received by Manufacturer (mo/day/yr)		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____	
5. If IND, Give Protocol #		5. (A)NDA # _____ IND # _____ PLA # _____ Pre-1938 <input type="checkbox"/> Yes OTC <input type="checkbox"/> Yes Product <input type="checkbox"/> Yes	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> Periodic <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up # _____		8. Adverse Event Term(s)	
9. Manufacturer Report Number			

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event <input type="checkbox"/> Death <input type="checkbox"/> Serious Injury <input type="checkbox"/> Malfunction <input type="checkbox"/> Other: _____		2. If Follow-up, What Type? <input type="checkbox"/> Correction <input type="checkbox"/> Additional Information <input type="checkbox"/> Response to FDA Request <input type="checkbox"/> Device Evaluation	
3. Device Evaluated by Manufacturer? <input type="checkbox"/> Not Returned to Manufacturer <input type="checkbox"/> Yes <input type="checkbox"/> Evaluation Summary Attached <input type="checkbox"/> No (Attach page to explain why not) or provide code: _____		4. Device Manufacture Date (mo/yr)	
6. Evaluation Codes (Refer to coding manual) Method _____ Results _____ Conclusions _____		5. Labeled for Single Use? <input type="checkbox"/> Yes <input type="checkbox"/> No	
7. If Remedial Action Initiated, Check Type <input type="checkbox"/> Recall <input type="checkbox"/> Notification <input type="checkbox"/> Repair <input type="checkbox"/> Inspection <input type="checkbox"/> Replace <input type="checkbox"/> Patient Monitoring <input type="checkbox"/> Relabeling <input type="checkbox"/> Modification/ Adjustment <input type="checkbox"/> Other: _____		8. Usage of Device <input type="checkbox"/> Initial Use of Device <input type="checkbox"/> Reuse <input type="checkbox"/> Unknown	
9. If action reported to FDA under 21 USC 360(f), list correction/removal reporting number: _____			
10. <input type="checkbox"/> Additional Manufacturer Narrative		and/or 11. <input type="checkbox"/> Corrected Data	

The public reporting burden for this collection of information has been estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

OMB Statement:
"An agency may not conduct or sponsor,
and a person is not required to respond
to, a collection of information unless it
displays a currently valid OMB control
number."

FORM FDA 3500A (9/03) (Back)

Please DO NOT RETURN this form to this address

Figure 9.3. (Continued).

SPONTANEOUS REPORTING IN THE UNITED STATES

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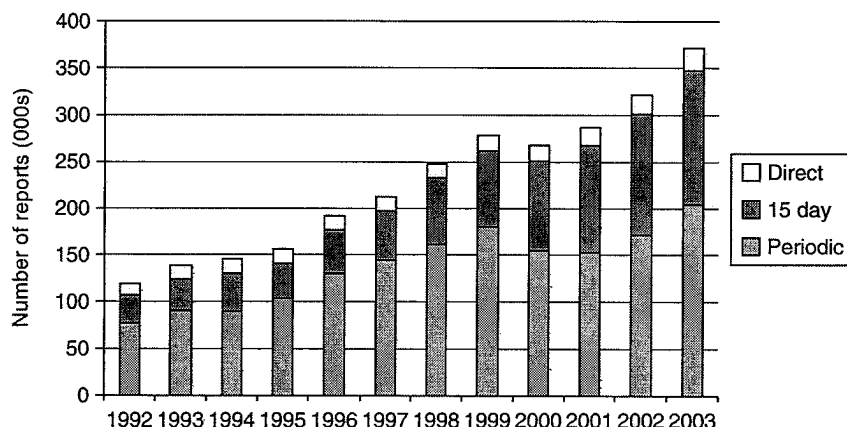


Figure 9.4. ADE reports by year and type, 1992–2003.

Table 9.1. Mandatory AE reporting requirements for pharmaceuticals

15-day "Alert Reports"	All serious and unexpected AEs, whether foreign or domestic, must be reported to the FDA within 15 calendar days
15-day "Alert Reports" follow-up	The manufacturer must promptly investigate all AEs that are the subject of a 15-day Alert Report and submit a follow-up report within 15 calendar days
Periodic AE reports	All non-15-day, domestic, AE reports must be reported periodically (quarterly for the first 3 years after approval, then annually). Periodic reports for products marketed prior to 1938 are not required. Periodic reporting does not apply to AE information obtained from postmarketing studies or from reports in the scientific literature
Scientific literature	A 15-day Alert Report based on information from the scientific literature (case reports or results from a formal clinical trial). A copy of the published article must accompany the report, translated into English if foreign
Postmarketing studies	No requirement for a 15-day Alert Report on an AE acquired from a postmarketing study <i>unless</i> manufacturer concludes a reasonable possibility that the product caused the event

important. To help promote reporting and tracking of adverse events associated with dietary supplements, the FDA's Center for Food Safety and Nutrition (CFSAN) launched its CFSAN Adverse Event Reporting System (CAERS) in the summer of 2003.¹⁹

The specific regulations governing postmarketing AE reporting by pharmaceutical companies are listed in Table 9.2. Accompanying separate guidances for drugs and biologics were made available in 1992²⁰ and 1993,²¹ respectively. As can be seen, the regulations have each been amended numerous times.

Many of the proposed rules, draft guidance documents, and a docket memo (in various stages of development) encourage electronic AE reporting. Electronic reporting

is an important step because reports are available for review more quickly. Further, electronic reporting reduces data entry costs, allowing the Center for Drug Evaluation and Research (CDER) to use its resources for additional pharmacovigilance efforts. The proposed rules, draft guidances, and docket memo and their associated statutes are as follows:

- The proposed rule on Adverse Event Reporting and guidance on electronic submissions are currently being finalized.
- A draft Guidance for Industry, "Providing Regulatory Submissions in Electronic Format—Postmarketing Expedited Safety Reports," was released in May 2001.

Table 9.2. Federal regulations regarding postmarketing adverse event reporting

21 CFR 310.305 Prescription drugs not subject to premarket approval	[July 3, 1986 (51 FR 24779), amended October 13, 1987 (52 FR 37936); March 29, 1990 (55 FR 1578); April 28, 1992 (57 FR 17980); June 25, 1997 (62 FR 34167); October 7, 1997 (62 FR 52249); March 4, 2002 (67 FR 9585)]
21 CFR 314.80 Human drugs with approved new drug applications (NDAs)	[February 22, 1985 (50 FR 7493) and April 11, 1985 (50 FR 14212), amended May 23, 1985 (50 FR 21238); July 3, 1986 (51 FR 24481); October 13, 1987 (52 FR 37936); March 29, 1990 (55 FR 11580); April 28, 1992 (57 FR 17983); June 25, 1997 (62 FR 34166, 34168); October 7, 1997 (62 FR 52251); March 26, 1998 (63 FR 14611); March 4, 2002 (67 FR 9586)]
21 CFR 314.98 Human drugs with approved abbreviated new drug applications (ANDAs)	[April 28, 1992 (57 FR 17983), amended January 5, 1999 (64 FR 401)]
21 CFR 600.80 Biological products with approved product license applications (PLAs)	[October 27, 1994 (59 FR 54042), amended June 25, 1997 (62 FR 34168); October 7, 1997 (62 FR 52252); March 26, 1998 (63 FR 14612); October 20, 1999 (64 FR 56449)]

- A memo entitled, "Postmarketing Expedited Safety Reports—15-Day Alert Reports," was added to public Docket 92S-0251 on May 22, 2002. This memo allows for voluntary electronic reporting of 15-day (expedited) safety reports with no paper submissions required.
- A draft Guidance for Industry entitled, "Providing Regulatory Submissions in Electronic Format—Postmarketing Periodic Adverse Drug Experience Reports," was published on June 24, 2003.

As of the end of 2003, nearly 20% of all expedited reports were submitted electronically, and the FDA encourages firms to participate in this voluntary process, replacing Med-Watch (3500A) reports. To facilitate this effort, the FDA hosts a meeting twice yearly with representatives from major pharmaceutical firms. The purpose of this meeting is to discuss electronic AE reporting, including ways to stimulate increased electronic reporting within the industry. A description of the process of how the FDA handles these reports will be provided in a later section of this chapter.

Recent Changes

In recent years, there has been a significant international effort to standardize the pharmaceutical regulatory environment worldwide through the auspices of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. These efforts toward international harmonization have a direct impact on how the FDA is currently rewriting regulations on AE reporting. AERS was launched in November 1997 and is an internationally compatible system in full accordance with the ICH initiatives.

The initiatives that directly affect postmarketing surveillance are:

- M1 IMT (International Medical Terminology): AERS uses the Medical Dictionary for Regulatory Activities (MedDRA) as its coding tool for reported adverse reaction/adverse event terms via individual case safety reports.
- M2 ESTR1 (Electronic Standards for the Transfer of Regulatory Information): AERS uses ESTR1 standards for submission of individual case safety reports in electronic form via the electronic data interchange (EDI) gateway.
- E2B(M) (Data Elements for Transmission of Individual Case Safety Reports): AERS has implemented the E2B data format into its database, and will use the E2B as the standard for electronic submissions.
- E2C PSUR (Periodic Safety Update Reports): defines a standard format for clinical safety data management for PSURs for marketed drugs. Initially, PSURs will be submitted on paper, and the FDA has published guidance to allow these summaries to be sent in electronically to the electronic Central Document Room (eCDR).

The Agency has undertaken a major effort in implementation of the electronic reporting of Individual Case Safety Reports (ICSRs) based on the ICH E2B(M), M1 (MedDRA), and M2 standards, and to clarify and revise its regulations regarding pre- and postmarketing safety reporting requirements for human drug and biologic products. In the *Federal Register* of October 7, 1997 (62 FR 52237), the FDA published a final rule amending its regulations for expedited safety reporting. This final rule implements the ICH E2A initiative on clinical safety data management. Based on E2A, the final rule provides an internationally accepted definition of

“serious,” requires the submission of the MedWatch 3500A for paper submissions, requires expedited reports in a 15 calendar rather than working day time frame, and harmonizes procedures for reporting pre- and postmarketing as well as international and domestic reporting. With regard to the postmarketing safety reporting regulations for human drug and licensed biologic products, the Agency published a proposed rule in the *Federal Register* of October 27, 1994 (59 FR 54046), to amend these requirements, as well as others, to implement international standards, and to facilitate the reporting of adverse experiences.

To help the pharmaceutical manufacturers understand the new requirements, on August 27, 1998 the FDA published an interim guidance for industry, “Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Clarification of What to Report.”

In the *Federal Register* of November 5, 1998 (63 FR 59746), the Agency published an Advanced Notice of Proposed Rulemaking to notify manufacturers that it is considering preparing a proposed rule that would require them to submit individual case reports electronically using standardized medical terminology, standardized data elements, and electronic transmission standards as recommended by ICH in the M1, M2, and E2B(M) initiatives. The FDA published a Public Docket 92A-0251, “Electronic Submission of Postmarketing Expedited Periodic Individual Case Safety Reports,” which allows pharmaceutical companies to submit reports to the FDA electronically.

In March 2001, the Agency issued a “Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines,” which superseded the March 1992 document.

The November 2001 Guidance for Industry “Electronic Submission of Postmarketing Expedited Safety Reports,” describes how pharmaceutical companies may submit ICSRs using EDI gateway and physical media (e.g., CD-ROM) and attachments to ICSRs using only physical media.

In May 2002, the FDA issued a Guidance for Industry “Providing Regulatory Submissions in Electronic Format—Postmarketing Periodic Adverse Drug Experience Reports,” which describes how pharmaceutical companies may submit periodic ICSRs with and without attachments and descriptive information (including PSURs) using physical media.

In September 2003, the FDA issued a Guidance for Industry “Providing Regulatory Submissions in Electronic Format—Annual Reports for NDAs and ANDAs,” which describes how pharmaceutical companies may submit descriptive information (including PSURs) using physical media.

On October 1, 2003, the FDA transferred certain product oversight responsibilities from the Center for Biologics

Evaluation and Research (CBER) to the CDER. This consolidation provides greater opportunities to further develop and coordinate scientific and regulatory activities between CBER and CDER, leading to a more efficient and consistent review program for human drugs and biologics. The FDA believes that as more drugs and biologic products are developed for a broader range of illnesses, such interaction is necessary for both efficient and consistent agency action. Under the new structure, the biologic products transferred to CDER will continue to be regulated as licensed biologics.

PROPOSED MODIFICATIONS

At the current time, the FDA is working on further modifications to the postmarketing safety reporting requirements. A Serious Adverse Drug Reaction (SADR) Reporting Proposed Rule is expected to be published in the near future, that focuses on report quality, standardizes terminology to “Adverse Drug Reaction,” and encourages active query by health care professional at the company who speaks directly with the initial reporter of the serious adverse reaction report. This entails, at a minimum, a focused line of questioning designed to capture clinically relevant information, follow-up, and determination of seriousness, and defines the minimum data set for safety reports. The proposed rule will also implement the ICH E2C: International PSUR, which contains marketing status, core labeling (company core data sheet (CCDS); company core safety information (CCSI) is safety information in CCDS), changes in safety status since last report, exposure data, clinical explanation of cases, data line (narrative summary of the individual case safety reports which provide demographic, drug, and event information) listings and tables, status of postmarketing surveillance safety studies, overall critical analyses, and assessments. The earlier October 27, 1994 proposed amendments to the postmarketing periodic AE reporting requirements will be repropounded in this current Proposed Rule, based on a guidance on this topic developed by ICH.²²

As noted previously, OTC products without an NDA are not subject to reporting. To bring these products into the postmarketing safety net, the FDA plans to publish an OTC ADR Reporting Proposed Rule. Consideration is being given to the requirement for ADR reporting for OTC monograph drugs, since most marketed OTC drugs lack an approved NDA. The FDA’s review of marketed OTC drugs without approved NDAs (ANDAs) has been accomplished through rulemaking establishing conditions in OTC drug monographs for drugs within therapeutic classes (e.g., laxatives). An OTC drug monograph specifies the conditions (i.e., ingredients and concentrations, testing procedures, dosage, labeling, and

mode of administration) under which an OTC drug is generally recognized as safe and effective and is not misbranded.

In an effort to expand the Agency's ability to monitor and improve the safe use of human and biologic products both during clinical trials and once the products are on the market, the FDA on March 14, 2003 published a proposed rule, titled "Safety Reporting Requirements for Human Drug and Biological Products" ("*The Tome*"), which would require companies to file expedited reports of suspected ADRs unless the company is certain the product did not cause the reaction.

The Tome recommended the replacement of periodic drug adverse experience reports (21 CFR 314.80) with PSURs. Currently, CDER encourages industry to submit a waiver to allow submission of PSURs instead of periodic drug adverse experience reports. PSURs are in the format proposed by the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, Topic E2C. The PSUR summarizes the safety data received by a sponsor for an application from worldwide sources for a specific time frame. The number of PSURs received is dependent on the number of NDAs/ANDAs marketed. The PSUR format enhances postmarketing drug and therapeutic biologic safety because it requires additional information and analyses (such as patient exposure data) not required in the periodic adverse drug experience report. These additional data enhance our review of postmarketing safety.

DATA COLLECTION: THE MEDWATCH PROGRAM

An effective national postmarketing surveillance system depends on voluntary reporting of adverse events, medication errors, and product quality problems by health professionals and consumers to the FDA, either directly or via the manufacturer. Neither individual health professionals nor hospitals are required by Federal law or regulation to submit AE reports on pharmaceuticals, although Federal law does require hospitals and other "user facilities" to report deaths and serious injuries that occur with medical devices.²³

Many health care organizations recommend and promote the reporting of AEs to the FDA. Adverse event monitoring by hospitals is included in the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) standards for patient safety issued in 2003. In order to maintain full accreditation, JCAHO requires each health care organization to monitor for adverse events involving pharmaceuticals and devices, with medication monitoring to be a continual collaborative function. JCAHO standards indicate that medical product AE reporting should be done per applicable law/regulation, including those of state/Federal bodies.²⁴

The FDA encourages all health care providers (physicians, pharmacists, nurses, dentists, and others) to consider adverse event reporting to the FDA as part of their professional responsibility. The American Society of Health-System Pharmacists has issued guidelines on ADR monitoring and reporting.²⁵

The American Medical Association and American Dental Association advocate physician and dentist participation in adverse event reporting systems as an obligation.^{26,27} Since 1994, *The Journal of the American Medical Association* has instructed its authors that adverse drug or device reactions should be reported to the appropriate government agency, in addition to submitting such information for publication.²⁸ The International Committee of Medical Journal Editors have revised the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" to also encourage timely reporting of urgent public health hazards.²⁹

Given the vital importance of postmarketing surveillance, MedWatch, the FDA Safety Information and Adverse Event Reporting Program, was established in 1993.^{30,31} While the FDA's longstanding postmarketing surveillance program predates MedWatch, this outreach initiative to health care professionals and patients was designed to promote and facilitate the voluntary reporting process by both health care providers and their patients.

The MedWatch program has four goals. The first is to increase awareness of drug, device, and other medical product-induced disease and the importance of reporting. Health professionals are taught that no drug or other medical product is without risk and are encouraged to consider medical products as possible causes when assessing a clinical problem in a patient. This goal is accomplished through educational outreach, which includes professional presentations, publications, and a continuing education program.³²

The second goal of MedWatch is to clarify what should be reported. Health professionals and their patients are encouraged to limit reporting to serious AEs, enabling the FDA and the manufacturer to focus on the most potentially significant events. Causality is not a prerequisite for reporting; suspicion that a medical product may be related to a serious event is sufficient reason to notify the FDA and/or the manufacturer.

The third goal is to make it convenient and simple to submit a report of a serious AE, medication error, or product quality problem directly to the FDA. A single-page form is used for reporting suspected problems with all human-use medical products (except vaccines) regulated by the Agency—drugs, biologics, medical devices, special nutritionals (e.g., dietary supplements, medical foods, infant formulas), and cosmetics. There are two versions of the form (see Figures 9.2 and 9.3). The FDA form 3500 is used for voluntary reporting, while the FDA form 3500A is used for mandatory

reporting. Both forms are available on the FDA MedWatch website (<http://www.fda.gov/medwatch>) and may be downloaded as fillable forms for saving and printing. The postage-paid FDA 3500 form may be returned to the FDA by mail or by fax to 1-800-FDA-0178.

In 1998, the MedWatch program implemented an online version of the voluntary FDA 3500 form for reporting via the Internet (see www.fda.gov/medwatch). In 2003, about 40% of the direct (voluntary) reports received from providers and consumers were sent to the FDA via this online application. In addition, MedWatch provides a toll-free 800 phone number, 1-800-FDA-1088, for reporters who wish to submit a report verbally to a MedWatch health professional.

Vaccines are the only FDA-regulated human-use medical products that are not reported on the MedWatch reporting form. Reports concerning vaccines are sent to the vaccine adverse event reporting system (VAERS) on the VAERS-1 form, available by calling 1-800-822-7967 or from the VAERS website at www.fda.gov/cber/vaers/vaers.htm. VAERS is a joint FDA/Center for Disease Control and Prevention program for mandatory reporting by physicians of vaccine-related adverse events (see also Chapter 30).

The FDA recognizes that health professionals have concerns regarding their confidentiality as reporters, and that of the patients whose cases they report. In order to encourage reporting of adverse events, FDA regulations offer substantial protection against disclosure of the identities of both reporters and patients. In 1995, a regulation went into effect strengthening this protection against disclosure by preempting state discovery laws regarding voluntary reports held by pharmaceutical, biological, and medical device manufacturers.³³ In addition, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (see www.fda.gov/medwatch/hipaa.htm) specifically permits pharmacists, physicians, or hospitals to continue to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products (see also Chapter 38).

Manufacturers who participate in the FDA "MedWatch to Manufacturer" program (MMP) are provided with copies of serious reports submitted directly to the FDA for new molecular entities (see www.fda.gov/medwatch). To facilitate obtaining follow-up information, health professionals who report directly to the FDA are asked to indicate whether they prefer that their identity not be disclosed through the MMP to the manufacturer of the product involved in the case being reported. When such a preference is indicated, this information will not be shared.

The fourth goal of MedWatch is to provide timely and clinically useful safety information on all FDA-regulated medical products to health care professionals and their patients. The

FDA's interest in informing health professionals about new safety findings is not only to enable them to incorporate new safety information into daily practice, but also to demonstrate that voluntary reporting has a definite clinical impact.

As new information becomes available through "Dear Health Professional Letters," public health advisories and safety alerts, it is posted on the MedWatch website and immediate notification of the posting is sent by email to subscribers of the MedWatch listserve. This listserve reaches health care professionals, consumers, and the media. In 2004, MedWatch disseminated new safety information on over 45 drug or therapeutic biologic products as "safety alerts" to over 45 000 individual subscribers. One can subscribe to the MedWatch listserve by visiting the website (<http://www.fda.gov/medwatch/elist.htm>).

MedWatch also has a network of more than 160 health care professional, health care consumer and health care media organizations that have allied themselves with the FDA as MedWatch Partners. Each of these organizations works with MedWatch to promote voluntary reporting and disseminate safety information notifications to their members or subscribers by using their websites, email distribution lists, and publications such as bulletins and journals.

SAFETY ASSESSMENT: THE ADVERSE EVENT REPORTING SYSTEM (AERS)

AERS is a client-server, Oracle-based relational database system that contains all AE reports on pharmaceuticals submitted to the Agency either directly or via the manufacturer. The mission of AERS is to reduce adverse events related to FDA-regulated products by improving postmarketing surveillance and helping to prevent adverse outcomes related to medical errors.

AERS was designed and implemented with the following concepts in mind:

- friendly screen layout and help function;
- enhanced search capabilities, quality control features and electronic review of reports;
- improve the operational efficiency, effectiveness, and quality control of the process for handling AEs;
- improve the accessibility of AE information to all safety evaluators and medical officers within the FDA;
- implement and maintain compatibility with ICH standards;
- build the capability to receive electronic submissions of AEs using ICH standards;
- provide automated signal generation capabilities and improved tools for the analysis of potential AE signals.

Pharmaceutical manufacturers submit paper AE reports to the FDA central document room, where they are tracked and forwarded to the Office of Drug Safety (ODS) in the FDA's CDER. Reports submitted by individuals are mailed, faxed, sent via the Internet, or phoned into MedWatch, and are triaged to the appropriate FDA Center(s) (i.e., CDER, CBER, Center for Devices and Radiological Health (CDRH), Center for Veterinary Medicine (CVM), and CFSAN).

When received by the ODS, these incoming 3500 and 3500A reports are assigned a permanent report number (individual safety report), imaged, and stored in a Retrieval-Ware Imaging System; subsequently they are entered verbatim into the AERS database. Data entry has a number of sequential steps involving comparative entry, quality comparison of critical entry fields, and coding and quality control into standardized international medical terminology using MedDRA. Direct and 15-day expedited reports receive priority handling and are entered into AERS within 14 days.

Automated quality control is performed to review reports for timeliness, completeness, and accuracy of coding. Statistical samples are also used to spot check manufacturer performance in providing accurate and timely reports, which can be used for compliance functions.

Although the bulk of the data entry into AERS is currently done through manual coding, AERS is designed for electronic submission of ICH E2B(M) standardized, MedDRA precoded individual case safety reports. This design concept incorporates the ICH standards for content, structure, and transmittal of individual case safety reports. To prepare for full-scale implementation of electronic submissions, a step-by-step pilot program was in place. The pilot moved into full production in 2002 for capturing ICSRs.

Copies of all reports in the AERS database are available to the public through the FDA Freedom of Information Office, with all confidential information redacted (e.g., patient, reporter, institutional identifiers). The AERS database, in non-cumulative quarterly updates, can be obtained from the National Technical Information Service (www.NTIS.gov) or from the FDA website (www.fda.gov/cder/aers/extract.htm).

A variety of technology-assisted features in the AERS augment the AE review by the ODS's safety evaluators. Safety evaluators have the following pharmacovigilance tools available for AE report screening to generate signals:

- *Primary triage*: the program screens incoming reports and alerts safety evaluators to serious and unlabeled events, and serious medical events known to be drug-related (e.g., *torsade de pointes*, agranulocytosis, toxic epidermal necrolysis, etc.).

- *Secondary triage/surveillance*: provides a tool for signal identification based on overall specific counts for each risk category associated with all ADR reports received for a given drug.
- *Periodic (canned) reports*: enables periodic reviews of the AERS database, including all new actions in a time period.
- *Active (canned and/or ad hoc) query*: represents active investigation of case series signals found from any of the above levels of screening.

The AERS maximizes the ability of the Agency to identify and assess signals of importance in the spontaneous reporting system. Starting in 2004 and over a 5-year period, these upgrades will occur in what we are calling AERS II. AERS will be upgraded to handle the FDA's processing of post-marketing adverse event reports related to human drugs and therapeutic biologics over the next 5 years. It will be web based, accept electronic submissions, meet ICH, HL7, E2B(M), eXtensible Markup Language (XML), and Tagged Image File Format (TIFF) requirements; handle multiple product coding schemes (bar codes), interface to industry and other government systems, and include a reporting repository providing pre-tailored reports and an ad hoc feature for specialized needs.

FDA EVALUATION OF REPORTS OF ADVERSE EVENTS

Every single workday, the FDA receives nearly one thousand spontaneous reports of adverse events either directly or through the industry. The ODS in CDER employs about 25 postmarketing safety evaluators and over a dozen epidemiologists.

The primary duty of safety evaluators is to review adverse event reports. Most of the safety evaluators are clinical pharmacists who are assigned specific groups or classes of drugs or therapeutic biologic products based on their past training and/or experience. These safety evaluators work under the tutelage and guidance of about half a dozen team leaders who have considerable experience in the evaluation and assessment of adverse event reports, substantial knowledge of the drug or therapeutic biologic agent, and awareness of the limitations of the AERS data. Every serious labeled or unlabeled adverse event report or reports describing important medical events such as liver failure, cardiac arrhythmias, renal failure, and rhabdomyolysis are electronically transferred into the computer inbox of the safety evaluators, who monitor these events daily. The safety evaluators try to identify a potential "signal," which is defined as a previously unrecognized or unidentified serious adverse event.

Epidemiologists within the ODS are medical/clinical epidemiologists with MDs/MPHs or PhDs. Medical epidemiologists help in the “signal” development by evaluation of potential adverse event case reports (numerator data) and identification of risk factors/confounders. Epidemiologists are frequently asked to quantify and describe the exposed population (denominator data). Epidemiologists also critique published and unpublished epidemiologic studies, and participate in the design and development of protocols for epidemiologic studies submitted by drug companies in areas of regulatory interest.

The essential elements of a case report include drug name, concise description of the adverse event, date of onset of the event, drug start/stop dates, if applicable, baseline patient status (comorbid conditions, use of concomitant medications, presence of risk factors), dose and frequency of administration, relevant laboratory values at baseline and during therapy, biopsy/autopsy reports, patient demographics, de-challenge (event abates when the drug is discontinued) and re-challenge (event recurs when drug is restarted), and information about confounding drugs or conditions where available. For example, in a report describing hepatotoxicity, baseline information about liver status and information about liver enzyme monitoring would be considered essential.³⁴

If a “signal” is noted, the safety evaluator may try to find additional cases by querying the AERS database, doing literature searches, contacting foreign regulatory agencies directly, or collecting cases through the World Health Organization (WHO) Uppsala Monitoring Centre in Sweden. If the report is poorly documented, the safety evaluator may contact the reporter or the manufacturer for follow-up information. A case definition may be developed in collaboration with an epidemiologist and refined as new cases are identified. After a case series is assembled, the safety evaluator may look for common trends, potential risk factors, or any other items of importance. Meanwhile, with the help of drug utilization specialists in the ODS, drug usage data is obtained for the relevant drug or class of drugs or drugs within the same therapeutic category. Drug usage data are used in a variety of ways, including to obtain demographic information on the population exposed to pharmaceutical products, average duration and dose of dispensed prescription, and the specialty of the prescribing physicians. These data allow the FDA to examine how long non-hospitalized patients stay on prescription medication therapy and to learn drug combinations that may be prescribed to the same patients concurrently. These data are also used in association with AERS data to understand the context within which ADEs occur. Additionally, one or more epidemiologists

may be consulted to find the background incidence of the adverse outcome in question and to estimate the reporting rates of the adverse outcome, and compare it with the background rate at which the same event occurs in the population. Simply stated, a reporting rate is the number of reported cases of an adverse event of interest divided by some measure of the suspect drug’s utilization, usually the number of dispensed prescriptions.³⁵ If the issue is of regulatory importance, it may be brought to the attention of others within the ODS by presentation at one of the two in-house ODS forums, the Safety Evaluator Forum and the Epi Forum. At these forums relevant personnel from the review divisions in the CDER Office of New Drugs may be invited since they are ultimately responsible for regulatory actions involving the marketing status of the product. The review division may request manufacturer-sponsored postmarketing studies to further evaluate the issue. Simultaneously, epidemiologists in the ODS may explore the feasibility of conducting pharmacoepidemiology studies in one or more large claims database(s) that link prescriptions with medical records. The FDA has funded extramural researchers through a system of cooperative agreement for more than a decade. These investigators have access to large population-based databases and the FDA utilizes their resources to answer drug safety questions and to study the impact of regulatory decisions.

After confirmation of a “signal” the FDA can initiate various regulatory actions, the extent and rigor of which depend on the seriousness of the adverse event, the availability, safety, the acceptability of alternative therapy, and the outcome of previous regulatory interventions.⁴ Regulatory interventions to manage the risk include labeling change such as a boxed warning, restricted use or distribution of the drug, name or packaging change(s), a “Dear Health Care Professional” letter, or, rarely, possible withdrawal of a medical product from the market (see Table 9.3 and also Chapter 33).

The time between the first identification of a safety risk and the implementation of a regulatory action may take several months to years depending on the nature of the problem and the public health impact. For example, several years elapsed between the time when dangerous drug interactions with cisapride and a number of other drugs were identified and when the drug was ultimately removed from the market for general use. Similarly, severe liver failure in association with the use of the antidiabetic drug troglitazone was noted a few months after marketing but it took a few years before the drug was removed from the market. In the examples of both cisapride and troglitazone, a variety of regulatory interventions, such as repeated labeling changes and “Dear Health Care Professional” letters, were applied over the years

Table 9.3. Recent safety-based drug withdrawals

Drug name	Year approved/year withdrawn
Phenylpropanolamine	—/2000 (never approved by FDA)
Fenfluramine	1973/1997
Terfenadine	1985/1998
Astemizole	1988/1999
Cisapride	1993/2000
Dexfenfluramine	1996/1997 (not an NME)
Bromfenac	1997/1998
Cerivastatin	1997/2001
Grepafloxin	1997/1999
Mibefradil	1997/1998
Troglitazone	1997/2000
Rapacuronium	1999/2001
Rofecoxib	1999/2004
Alosetron*	2000/2000
Valdecoxib	2001/2005

* Returned to market in 2002 with restricted distribution.

to manage the risk before these products were removed from the market. These regulatory interventions did not achieve meaningful improvement in prevention of contraindicated drug use or in liver enzyme testing, respectively.^{36,37}

To notify health professionals of important new safety information discovered after marketing, the FDA often requests that the manufacturer send a “Dear Health Care Professional” letter to warn providers of particular safety issues. This is done in combination with a labeling change, although only a small proportion of labeling changes result in such letters. Frequently, the change in labeling may be accompanied by issuance of a press release (also known as a Talk Paper) or public health advisory. Additionally, FDA scientists may disseminate new drug safety information through publications in professional journals^{38–65} and presentations at professional meetings.

There were 43 drug or biologic letters/safety notifications posted in 2002 and 36 in 2003. In 2003, safety-related labeling changes were approved by the FDA for 20–45 drug products each month. “Dear Health Care Professional” letters and other safety notifications, and summaries of safety-related labeling changes approved each month, can be found on the MedWatch website (www.fda.gov/medwatch/safety.htm). Table 9.4 lists some examples of recent “Dear Health Care Professional” letters.

The FDA can seek to restrict or limit the use of a drug product through labeling if the adverse reaction associated with the drug has severe consequences. For example, the labeling for the new arthritis/pain drug valdecoxib was strengthened with new warnings following postmarketing

reports of serious adverse effects, including life-threatening risks related to skin reactions—including Stevens–Johnson Syndrome, and anaphylactoid reactions. The labeling now advises people who start valdecoxib and experience a rash to discontinue the drug immediately and also the drug is contraindicated in patients allergic to sulfa-containing products. The drug has recently been removed from the market.

Drug safety problems can also lead to the removal of a drug from the market. Fortunately, such product withdrawals are very uncommon; there have been only 22 drugs taken off the US market since 1980; drugs withdrawn recently are listed in Table 9.3.

In addition to the technology used in current adverse event reporting, including sophisticated relational databases and network connections for electronic transfer, new methods to evaluate and assess spontaneous reports are being explored to take advantage of the sheer volume of data. Aggregate analysis tools and data mining techniques are currently being developed by ODS, WHO,⁶⁶ and others, to systematically screen large databases of spontaneous reports.

Since 1998, the FDA has explored automated and rapid Bayesian data mining techniques to enhance its ability to monitor the safety of drugs, biologics, and vaccines after they have been approved for use.⁶⁷ In May 2003, the FDA announced the establishment of a Cooperative Research and Development Agreement (CRADA) with a private software development company. The CRADA is expected to improve the utility of safety data mining technology. The FDA’s CDER and CBER will work with this private company to develop new and innovative ways for extracting information related to drug safety and risk assessment. To this end, a desktop data mining software tool, called WebVDME, has been developed and is currently being piloted.

Data mining is a technique for extracting meaningful, organized information from large complex databases. In data mining the strategy is to use a computer to identify potential signals in large databases that might be overlooked, for a variety of reasons, in a manual review on a case-by-case basis. Drug–AE signals are generated by comparing the frequency of reports with what would be expected if all drugs and AEs were assumed to follow certain patterns. The goal is to distinguish the more important or stronger signals to facilitate identification of combinations of drugs and events that warrant more in-depth follow-up. Data mining is a tool best suited for generation of possible signals and it cannot replace or override the meticulous hands-on review by safety evaluators. Further, whether it has any advantage over the hands-on review,

SPONTANEOUS REPORTING IN THE UNITED STATES

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Table 9.4. Recent FDA MedWatch safety alerts/"Dear Health Care Professional" letters, 2003

Drug	Details
Topamax® (topiramate)	Revised the WARNINGS and PRECAUTIONS to notify health care professionals that Topamax causes hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate). Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended.
Permax® (pergolide mesylate)	Revised the WARNINGS and PRECAUTIONS sections to inform health care professionals of the possibility of patients falling asleep while performing daily activities, including operation of motor vehicles, while receiving treatment with Permax®. Many patients who have fallen asleep have perceived no warning of somnolence.
Arava® (leflunomide)	In postmarketing experience worldwide, rare, serious hepatic injury, including cases with fatal outcome, have been reported during treatment with Arava. Most cases occurred within 6 months of therapy and in a setting of multiple risk factors for hepatotoxicity.
Viread® (tenofovir disoproxil fumarate)	Notified health care professionals of a high rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor resistance associated mutations in a clinical study of HIV-infected treatment-naïve patients receiving a triple regimen of didanosine, lamivudine and tenofovir disoproxil fumarate.
Lariam® (mefloquine hydrochloride)	Notified health care professionals of the Lariam Medication Guide developed in collaboration with the FDA to help travelers better understand the risks of malaria, the risks and benefits associated with taking Lariam to prevent malaria, and the potentially serious psychiatric adverse events associated with use of the drug.
Prandin® (repaglinide)	Revised the PRECAUTIONS/Drug Interaction section to inform health care professionals of a drug-drug interaction between repaglinide and gemfibrozil. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide.
Serevent Inhalation Aerosol® (salmeterol xinafoate)	New labeling includes a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in a recently completed large US safety study.
Ziagen® (abacavir)	High rate of early virologic non-response observed in a clinical study of therapy-naïve adults with HIV infection receiving once-daily three-drug combination therapy with lamivudine (Epivir, GSK), abacavir (Ziagen, GSK), and tenofovir (Viread, TDF, Gilead Sciences).
Genotropin® (somatropin [rDNA origin] for injection)	Fatalities have been reported with the use of growth hormone in pediatric patients with Prader-Willi syndrome with one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection.
Topamax® (topiramate) tablets/sprinkle capsules	Oligohidrosis (decreased sweating) and hyperthermia have been reported in topiramate-treated patients. Oligohidrosis and hyperthermia may have potentially serious sequelae, which may be preventable by prompt recognition of symptoms and appropriate treatment.
Risperdal® (risperidone)	Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of risperidone in elderly patients with dementia-related psychosis.
Avonex® (Interferon beta-1a)	Postmarketing reports of depression, suicidal ideation and/or development of new or worsening of pre-existing psychiatric disorders, including psychosis, and reports of anaphylaxis, pancytopenia, thrombocytopenia, autoimmune disorders of multiple target organs, and hepatic injury.

and the degree to which it generates false signals, remain to be evaluated.

STRENGTHS

LARGE-SCALE AND COST-EFFECTIVE

Two vital advantages of surveillance systems based on spontaneous reports are that they potentially maintain ongoing surveillance of all patients, and are relatively inexpensive.⁶⁸ Spontaneous reporting systems are the most common method used in pharmacovigilance to generate signals on new or rare adverse events not discovered during clinical trials.⁶⁹

GENERATION OF HYPOTHESES AND SIGNALS

Making the best possible use of the data obtained through monitoring underlies postmarketing surveillance.⁷⁰ Toward that goal, the great utility of spontaneous reports lies in *hypothesis generation*,⁷¹ with need to explore possible explanations for the adverse event in question. By raising suspicions,⁷² spontaneous report-based surveillance programs perform an important function, which is to generate *signals* of potential problems that warrant further investigation.

Assessment of the medical product–adverse event relationship for a particular report or series of reports can be quite difficult. Table 9.5 lists factors that are helpful in evaluating the strength of association between a drug and a reported adverse event.⁷³

The stronger the drug–event relationship in each case and the lower the incidence of the adverse event occurring spontaneously, the fewer case reports are needed to perceive causality.⁷⁴ It has been found that for rare events, coincidental drug–event associations are so unlikely that they merit little concern, with greater than three reports constituting a signal requiring further study.⁷⁵ In fact, it has been suggested that a temporal relationship between medical product and adverse event, coupled with positive de-challenge and re-challenge,

can occasionally make isolated reports conclusive as to a product–event association.⁷⁶ Biological plausibility and reasonable strength of association aid in deeming any association as causal⁷⁷ (see also Chapter 36).

However, achieving certain proof of causality through adverse event reporting is unusual. Confirmation of an association between a drug and an adverse reaction usually requires further additional studies.⁷⁸ Attaining a prominent degree of suspicion is much more likely, but still may be considered a sufficient basis for regulatory decisions.⁷⁴

OPPORTUNITY FOR CLINICIAN CONTRIBUTIONS

The reliance of postmarketing surveillance systems on health professional reporting enables an individual to help improve public health. This is demonstrated by one study that found direct practitioner participation in the FDA spontaneous reporting system was the most effective source of new ADR reports that led to changes in labeling.⁷⁶ Ensuring that the information provided in the adverse event report is as complete and in-depth as possible further enhances postmarketing surveillance. Thus, while possessing inherent limitations, postmarketing surveillance based on spontaneous reports data is a powerful tool for detecting adverse event signals of direct clinical impact.

WEAKNESSES

There are important limitations to consider when using spontaneously reported adverse event information. These limitations include difficulties with adverse event recognition, underreporting, biases, estimation of population exposure, and report quality.

ADVERSE EVENT RECOGNITION

The attribution of AEs (or any other medical product-associated adverse event) may be quite subjective and imprecise.⁷⁹ While an attribution of association between the medical product and the observed event is assumed by the reporters with all spontaneously reported events, every effort is made to rule out other explanations for the event in question. It is well known that placebos⁸⁰ and even no treatment⁸¹ can be associated with adverse events. In addition, there is almost always an underlying background rate for any clinical event in a population, regardless of whether there was exposure to a medical product.

Table 9.5. Useful factors for assessing causal relationship between drug and reported adverse events

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- Chronology of administration of agent, including beginning and ending of treatment and adverse event onset
 - Course of adverse event when suspected agent stopped (de-challenge) or continued
 - Etiologic roles of agents and diseases in regard to adverse event
 - Response to readministration (re-challenge) of agent
 - Laboratory test results
 - Previously known toxicity of agent
-

Reaching a firm conclusion about the relationship between exposure to a medical product and the occurrence of an adverse event can be difficult. In one study, clinical pharmacologists and treating physicians showed complete agreement less than half the time when determining whether medication, alcohol or “recreational” drug use had caused hospitalization.⁸²

Such considerations emphasize the crucial need for careful, thoughtful review of adverse event reports upon their receipt by the FDA or the manufacturer. It is through this process that causality, or at least a high degree of suspicion for a product–adverse event association, is put to the test (see also Chapter 36). Ultimately, formal pharmacoepidemiology studies are usually needed to strengthen the observed association.

UNDERREPORTING

Another major concern with any spontaneous reporting system is underreporting of adverse events.^{71, 77} The extent of underreporting is unknown and may be influenced by the severity of the event, the specialty of the reporter, how long the drug has been on the market, whether the event is labeled, and whether the drug is prescription or non-prescription.⁸³ It has been estimated that rarely more than 10% of serious ADRs, and 2–4% of non-serious reactions, are reported to the British spontaneous reporting program.⁷⁷ A similar estimate is that the FDA receives by direct report less than 1% of suspected serious ADRs.⁸⁴ This means that cases spontaneously reported to any surveillance program, which comprise the numerator, generally represent only a small portion of the number that have actually occurred. The impact of underreporting can be somewhat lessened if submitted reports, irrespective of number, are of high quality.

BIASES

Spontaneously reported information is subject to the influence of a number of biases. These include the length of time a product has been on the market, size of sponsors’ detail force, target population, health care providers’ awareness, the quality of the data, and publicity effects.^{85–89}

In addition, it has been observed that spontaneous reporting of adverse events for a drug tends to peak at the end of the second year of marketing and reporting declines thereafter (Weber effect).⁹⁰

In addition to these biases, it is possible that reported cases might differ from nonreported cases in characteristics such as time to onset or severity.⁷⁵

ESTIMATION OF POPULATION EXPOSURE

Compounding these limitations is the lack of denominator data, such as user population and drug exposure patterns,⁷⁵ that would provide an estimate of the number of patients exposed to the medical product, and thus at risk for the adverse event of interest. Numerator and denominator limitations make incidence rates computed from spontaneously reported data problematic,⁷⁵ if not completely baseless. However, even if the exposed patient population is not precisely known, estimation of the exposure can be attempted through the use of drug utilization data.⁹¹

This approach, whose basic methodologies are applicable to medical products in general, can be of utility. Major sources of data on the use of drugs by a defined population include market surveys based on sales or prescription data, third-party payers or health maintenance organizations, institutional/ambulatory settings, or specific pharmacoepidemiology studies.⁹¹ Cooperative agreements and contracts with outside researchers enable the FDA to use such databases in its investigations (see Part IIIb). Care must be taken in interpreting results from studies using these databases. That drug prescribing does not necessarily equal drug usage,⁹¹ and the applicability of results derived from a specific population (such as Medicaid recipients) to the population at large, need to be weighed carefully.

REPORT QUALITY

The ability to assess, analyze, and act on safety issues based on spontaneous reporting is dependent on the quality of information submitted by health professionals in their reports. A complete adverse event report should include the following:

- product name (and information such as model and serial numbers in the case of medical devices);
- demographic data;
- succinct clinical description of the adverse event, including confirmatory/relevant test/laboratory results;
- confounding factors such as concomitant medical products and medical history;
- temporal information, including the date of event onset and start/stop dates for use of medical product;
- dose/frequency of use;
- biopsy/autopsy results;
- de-challenge/re-challenge information;
- outcome.

SUMMARY

The major limitations of the FDA's AE reporting system reflect the fact that the data are generated in an uncontrolled and incomplete manner. Although manufacturers are legally required to submit AE reports to the FDA and some of those reports are based on formal studies, the majority of AEs originate with practicing physicians who may or may not notify the manufacturer or the FDA when they observe an AE in one of their patients. It appears that they generally do not choose to report AEs, and the number of reports that the FDA receives is not representative of the extent of adverse events that occur in the United States. The number of reports in the system is also influenced by a variety of other factors, such as the extent and quality of the individual manufacturer's postmarketing surveillance activities, the nature of the event, the type of drug, the length of time it has been marketed, and publicity in the lay or professional press. Because of these limitations, AE reports are primarily useful for hypothesis generating, rather than hypothesis testing. Ironically, the scientifically uncontrolled nature of AE reporting creates its greatest advantage—the ability to detect and characterize AEs occurring across a broad range of medical practice—as well as its most serious limitations.

PARTICULAR APPLICATIONS

OVERALL

The FDA's AERS contains almost 3 million reports, with the earliest dating back to 1969. While reporting levels remained fairly constant during the 1970s—about 18 000 reports were entered into the database in 1970, and slightly over 14 000 reports were added in 1980—reporting increased dramatically after 1992, as can be seen in Figure 9.4. By 1992, the annual number of reports had risen to 120 000, and in 2003 was over 370 000. Forty percent of these reports were serious and unexpected (i.e., 15-day).

As noted earlier, the AERS contains reports from a variety of sources. Reports may be from the United States or other countries. The suspected AEs may have been observed in the usual practice of medicine or during formal studies; case reports from the literature are also included. Reports come to the FDA either directly from health professionals or consumers, or from pharmaceutical manufacturers. The vast majority (over 90%) of adverse drug event reports are received by the FDA through the manufacturer, with the remainder received directly from health care professionals or consumers.

In 2003, of all voluntary reports sent directly to the FDA, 68% involved drugs, 14% medical devices, 12% drug quality problems, 3% biologics, and 3% dietary supplements. The sources were: 59% from pharmacists, 15% from physicians, 9% from nurses, and 6% from non-health professionals (with 11% source not given).

SPECIFIC EXAMPLES

Temafloxacin (Omniflox®): Withdrawn from Market

This oral antibiotic was first marketed in February 1992. During the first three months of its use, the FDA received approximately 50 reports of serious adverse events, including three deaths. These events included hypoglycemia in elderly patients as well as a constellation of multi-system organ involvement characterized by hemolytic anemia, frequently associated with renal failure, markedly abnormal liver function tests, and coagulopathy. When approved by the FDA, temafloxacin was already being used in Argentina, Germany, Italy, Ireland, Sweden, and the United Kingdom. However, the FDA's experience with this drug demonstrates the critical importance of postmarketing surveillance and the timely reporting of adverse events. Prior to FDA approval, slightly more than 4000 patients had received the drug in clinical trials, and temafloxacin was considered to have a side effect profile similar to other quinolone antibiotics. In its first three months of commercial marketing, many thousands of patients received the drug. Only after this much broader clinical experience did the serious side effects described above become apparent. Less than four months after its introduction into the marketplace, the drug was withdrawn.⁹²

Linezolid (Zyvox®): Serious, Unlabeled ADR Noted Shortly After Approval

Linezolid (Zyvox®), a synthetic antibacterial agent of the oxazolidinone class, was approved for use in April 2000. It is indicated for the treatment of adult patients with the following infections caused by susceptible strains of designated microorganisms: vancomycin-resistant *Enterococcus faecium*, including cases with concurrent bacteremia; nosocomial pneumonia; complicated and uncomplicated skin and skin structure infections; and community-acquired pneumonia, including cases with concurrent bacteremia.

At the time of approval, safety data were limited, based primarily on its use in controlled clinical trials. The most serious adverse event noted in the initial product labeling was thrombocytopenia, mentioned in the Precautions section and the Laboratory Changes subsection of the Adverse Reactions section.

As reported in the Animal Pharmacology section of the product labeling, linezolid had caused dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity, decreased hematopoiesis, and decreased levels of circulating erythrocytes, leukocytes, and platelets in animal studies.

Within the first six months the drug was on the market, four cases of red cell aplasia associated with its use were received by the FDA. In addition, six other cases suggestive of myelosuppression had been submitted, as well as two cases of sideroblastic anemia.

With the increasing number of cases being received by the FDA, an in-depth review of this problem was undertaken. AERS was searched for reports of hematologic toxicity associated with linezolid and a total of 27 reports were retrieved through September 20, 2000. These reports were reviewed to find any that may have been suggestive of myelosuppression but were not necessarily reported as such (e.g., reductions in white blood count, hemoglobin and hematocrit, and platelets). In addition to the four red cell aplasia cases, six additional cases suggestive of myelosuppression were identified:

- A bone marrow transplant recipient who had a delayed engraftment that was thought to be due to linezolid myelosuppression.
- Three cases reported as routine complete blood counts (CBC), revealing decreased white blood cells (WBC), hemoglobin and hematocrit, and platelets. Personal communication with the reporters in these three cases found no further follow-up such as bone marrow biopsy, nor progression to more serious disease.
- Two cases were received as direct reports; one described as bone marrow suppression and thrombocytopenia in a 65-year-old male and the other as pancytopenia in a 51-year-old female.

Because of the rapidity with which these cases were reported to the FDA in the short time linezolid had been on the market, and the relatively small estimated number of courses of therapy sold, the FDA and the manufacturer agreed to the addition of prominent warnings to be included in the labeling concerning the development of myelosuppression. Changes were made to the Warnings and Precautions sections to recommend to clinicians that:

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known,

when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

Valproic Acid (Depakote®): Increased Severity of Labeled ADR Noted After Many Years of Use

Valproic acid products, including Depakote®, Depakene®, and Depacon®, have been used in clinical care since FDA approval in 1978. Although pancreatitis was first listed in the package inserts of valproate products in 1981, as with most drugs, there was limited safety data on this product at the time of approval. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience.

Initially, these drugs were indicated for a narrow labeled use and a limited population. Over two decades, the product was used for a wider range of both on-label and off-label indications, and the population exposed to the drug included a broader population than that exposed during the pre-approval clinical trials. With this increased use, the FDA received a number of voluntary reports through the MedWatch spontaneous reporting system of more severe forms of pancreatitis, often hemorrhagic, sometimes fatal, and with a number of cases occurring in infants and adolescent children. Although this ADR, pancreatitis, was "labeled" or known, the increased severity of the condition prompted the ODS postmarketing surveillance staff and the review division to initiate an epidemiological investigation and the development of a case series. This evaluation demonstrated that the rate based upon the reported cases exceeded that expected in the general population and there were cases in which pancreatitis recurred after re-challenge with valproate. With the agreement of the manufacturer, the FDA approved new safety labeling changes to the Warnings and Precautions sections and modified a black box warning to inform clinicians and their patients:

Pancreatitis: cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be

symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternate treatment for the underlying medical condition should be initiated as clinically indicated (see warnings and precautions).

THE FUTURE

The systematic collection and evaluation of postmarketing reports of serious ADRs by the FDA has come a long way since its inception about 50 years ago. The May 1999 report to the FDA Commissioner *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*⁶ found that the postmarketing surveillance program currently in place performed well for the goal it was designed to achieve—the rapid detection of unexpected serious AEs. Yet, it should be remembered that spontaneous reporting, although invaluable, is only one tool used in managing medical product risk. The report recognized that the FDA's programs are not designed to evaluate the rate, or impact, of known adverse events. The report proposed several options for improving risk management, including expanding the use of automated systems for reporting, monitoring, and evaluating AEs, and increasing the Agency's access to data sources that would supplement and extend its spontaneous reporting system. This could include use of large-scale medical databases from health maintenance organizations to reinforce, support, and enhance spontaneous signals and provide background rates and descriptive epidemiology.

Since the 1999 report, the FDA has continued to work with academia and industry to address these recommendations. In recognition of the increasing importance of postmarketing surveillance and risk assessment in the regulatory setting, a variety of initiatives are under way within the FDA. In 2002, the ODS was created within the CDER, with its three divisions focusing on improved identification and epidemiologic evaluation of ADRs, the evaluation of medication errors, and further research and implementation of risk communication activities directed toward both health care professionals and patients. The recent reauthorization of the Prescription Drug Users Fee Act (PDUFA) in 2002 will, for the first time, allow the FDA to apply user fee funds to the postmarketing activities of the Agency. In anticipation of these expanded efforts the FDA has published several guidance documents on postmarketing risk evaluation, risk communication, and risk management (see www.fda.gov/bbs/topics/news/2004/NEW01059.html).

In 2003, the ODS initiated a formal, competitive process of direct access to longitudinal, patient-level, electronic medical record data which can be used to study ADRs. Acquisition of this resource will directly enhance the ODS's ability to achieve one of the FDA's strategic goals, i.e., improving patient and consumer safety. In addition, online access to this data resource will allow the ODS to conduct drug safety studies in large population-based settings.

The FDA's current and future efforts include the following: increasing the quality of incoming reports of adverse events with a focus on making the AERS more efficient; establishing global reporting standards; promoting speed of reporting and assessment through electronic reporting; exploring new assessment and data visualizing methodologies; and, finally, exploring tools beyond spontaneous reporting. The last initiatives involve identification and assessment of linked databases and registries which can be accessed to expand surveillance, provide confirmatory evidence for signals, assess regulatory impact of labeling changes through studies, and, in general, build on the known strengths of spontaneous reporting—signal generation of potentially important events.

In addition, the ODS will refine current techniques to assess drug risks through the development and evaluation of risk management programs. We will continue to consider appropriate risk communication tools in order to clearly articulate drug safety information to both health professionals and patients in a timely manner. Our goals for the next 3–5 years include plans to develop and establish “best practices” for risk management plans and to develop quantitative approaches to the review of postmarketing safety data.

In summary, spontaneous reporting of AEs provides an important cornerstone for pharmacovigilance in the US. Regulators and manufacturers of medical products worldwide are moving forward the “single safety message transmission” with global harmonization for data standards and data transmission, improvements in relational database systems, the development of new risk assessment methodologies, and increased access to other data resources, including computerized medical records, to improve our overall ability to manage risk from pharmaceuticals.

DISCLAIMER

The opinions expressed are those of the authors and do not necessarily represent the views of the FDA or the US Government.

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